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Pathophysiological targets in OA therapy

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Over the last decade, there have been several interesting advances in the treatment of osteoarthritis (OA). A clearer understanding of the pathophysiology of OA (Fig. 1) has facilitated the development of new approaches for treatments aimed at specifically and effectively retarding the progression of this disease.

Recently, the drugs used to treat OA have been classified as being either symptomatic or structure (disease) modifying. A better understanding of the mechanisms of joint damage and repair has led to the development of a new class of molecules that inhibits one or several OA catabolic processes, while some of the drugs now used are being evaluated for their potential to alter the degenerative process.

The following contains a review of data on new molecules currently under evaluation, with an emphasis on recent developments concerning a new class of agents and their potential therapeutic use in human OA. Following this is a description of the newly envisaged approach to deliver the biological agents that have demonstrated beneficial therapeutic properties.

To date, no drug having disease modifying activity is available to treat OA. Studies have revealed strong evidence that nitric oxide (NO) produced via the elevation of inducible NO synthase (iNOS) is injurious to OA joint tissues [1, 2], and that selective inhibition of this enzyme would provide a novel therapeutic approach to treatment. In experimental models of inflammatory arthritis and OA, treatment with compounds that inhibit iNOS activity either nonselectively or selectively has been shown to reduce the severity of pathological lesions.

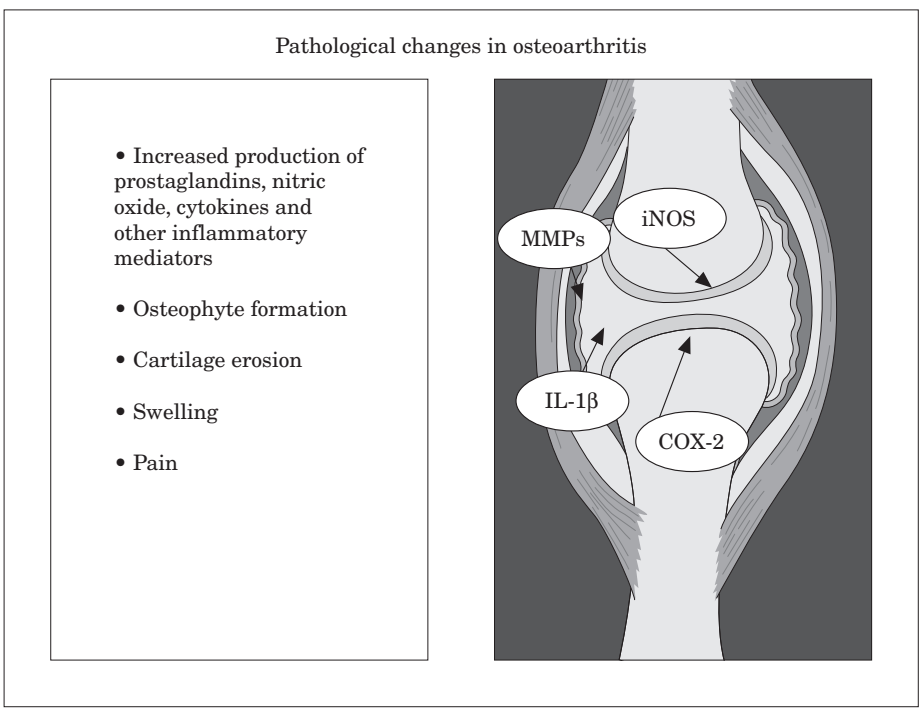

Fig. 1.

The proteolytic degradation of the extracellular matrix of cartilage in OA has been well documented, and metalloproteases (MMP) are believed to play a major role in this disease. Inhibition of the synthesis/activity of these enzymes as a treatment for OA has been the focus of intensive research [3]. Although there are natural biological inhibitors of MMP (e.g. tissue inhibiting metalloprotease; TIMP), their therapeutic use has been very limited due mainly to obstacles in the administration of proteins, and similar limitations exist for synthetic peptides. To date, the most promising agents are chemical molecules that can block the activity of MMP. Another attractive option to decreasing MMP levels is to interfere with the transcription factors of their promoter sequences. At present, factors under study act in a rather nonspecific manner.

A number of biological agents have also demonstrated potentially beneficial therapeutic properties both in-vitro and in some in-vivo models of arthritis including OA. These include proinflammatory cytokine inhibitors, cytokine soluble receptors and antiinflammatory cytokines. A major stumbling block in the use of biological molecules is the method used to deliver the agent and its applicability to the clinical scenario. Degradation of the protein after oral administration poses a problem, and if injected systematically, the large amount required and the need for frequent injections are often deterrents. This last route of administration can induce adverse effects including an immunological reaction with the appearance of a neutralizing antibody. The necessity of maintaining a sustained level of the agents over time is the major concern with this type of therapy.

In the last few years, much attention has been focused on the use of gene transfer techniques as a method of delivery. Many techniques have been developed using various genes, and a great deal of work is currently devoted to these techniques to facilitate the transfer of genes into joint cells and tissues, both *in vitro* and *in vivo*. The advantages of this approach in the treatment of OA are multiple, and include the identification of a very specific target, a consistently high local concentration in the joint of the therapeutic protein, and the maintenance of a sustained delivery over time. Moreover, there is hope that this type of therapy will reduce the incidence of side effects.

Two main systems, viral and non-viral, are currently used for gene transfer to cells. At this time, the viral system is favored for some proteins because it generally allows for a very effective transfer to a large percentage of cells while maintaining a sustained high level of protein expression that can be extended over significant periods of time.

Although the treatment of OA using gene therapy is very promising, this technique is still in the very early stage of development, and much work remains to be done, particularly on the in-vivo development of this technology for humans. Moreover, the selection of the gene(s) that would offer the best protection against OA remains
to be determined. Some proteins such as the interleukin-1 receptor antagonist (IL-1Ra) have elicited much attention in OA therapy, and results of these studies are now emerging.

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